40. (New) The method of claim 1, 2 or 17 wherein the mammal is genetically divergent at the immune response loci.

Remarks

Reconsideration and withdrawal of the rejections of the claims in the above-identified application, in view of the amendments and remarks presented herein, is respectfully requested. Claims 14-15, 19-30 and 32-33 have been canceled, and claims 1-3, 8, 17, and 31 amended. Claims 34-40 are added. The pending claims are 1-14, 16-18, 31, and 34-40. The amendments to the claims are intended to clarify Applicant's invention and not intended to limit the equivalents to which any claim element may be entitled.

Claims 19-30 and 32-33 are canceled solely in response to the restriction requirement and without prejudice to their presentation in an appropriately-filed divisional application.

The amendments to claim 1 are supported by originally filed claims 1, 3 and 14-15.

The amendments to claim 2 are supported by originally filed claims 2 and 15.

The amendments to claims 3 and 8 are supported by originally filed claims 3 and 8, respectively.

The amendments to claim 17 are supported by originally filed claims 15 and 17, and by the specification at page 5, lines 1-2 and page 60, lines 24-25.

The amendments to claim 31 are supported by originally filed claim 31.

New claim 34 is supported by originally filed claims 3 and 8.

New claim 35 is supported by originally filed claim 4.

New claim 36 is supported by originally filed claim 5.

New claim 37 is supported by originally filed claim 9.

New claim 38 is supported by originally filed claim 10.

New claim 39 is supported by originally filed claim 33.

New claim 40 is supported at page 16, lines 9-13 of the specification.

The 35 U.S.C. §112, second paragraph, rejection

The Examiner rejected claims 3 and 8 under 35 U.S.C. §112, second paragraph, alleging that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The amendments to the claims render the Examiner's rejection moot. It is respectfully submitted that the pending claims are in conformance with 35 U.S.C. §112, second paragraph, and so Applicant respectfully requests that the Examiner withdraw the 35 U.S.C. §112, second paragraph, rejection of the claims.

The 35 U.S.C. §102(b) rejection

The Examiner rejected claims 1-3, 6, 8-9, 13-14, 17, and 31 under 35 U.S.C. §102(b) as being anticipated by Norman et al. (Am. J. Respir. Crit. Care Med., 154, 1623 (1996)). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

In the introduction of Norman et al., the authors relate that T cells and antibodies interact with different ligands on allergens (page 1623). For example, IgE antibodies attach to complex B cell epitopes that require intact tertiary structures, while T cell receptors respond to short peptides from the allergen embedded in surface mixed histocompatibility molecules on antigen presenting cells (page 1623). The authors suggest that in patients who are allergic to cats, T cell non-responsiveness might be induced by peptides representing T cell epitopes of allergens, although the authors caution that the peptides must be carefully selected to avoid peptides having tertiary structures recognized by IgE antibodies (page 1623).

To determine whether peptides having T cell epitopes can induce tolerance, humans known to be allergic to cats were subcutaneously injected with a combination of two T cell reactive peptides of Fel d 1, the principle allergen of cat dander. The two peptides, IPC-1 (corresponding to residues 7-33 of chain 1 of Fel d 1), and IPC-2 (corresponding to residues 29-55 of chain 1 of Fel d 1), had been characterized as having multiple dominant T cell epitopes (Norman et al. citing to Counsell et al., J. Allergy Clin. Immunol., 98, 884 (1996)) and Briner et al. (Proc. Natl. Acad. Sci. USA, 90, 7608 (1993), a copy of each is enclosed herewith).

Briner et al. reported results obtained from the subcutaneous administration of a number of Fel d 1 peptides, including IPC-1 and IPC-2, to $B6D_2F_1(H\text{-}2^{bxd})$ and $B6CBAF_1$ $(H\text{-}2^{bxa})$ mice. Of interest is that Briner et al. do not disclose any experiments in which the immune response to the peptides for the two strains is compared and so this reference provides no evidence that IPC-1 and IPC-2 comprise a universal T cell epitope.

Counsell et al. discloses that Fel-1 (i.e., IPC-1) and/or Fel 2 (i.e., IPC-2) stimulated a T cell response in 95% of T cell lines derived from 53 patients with cat allergy, and suggest that these peptides may be useful in immunotherapy. Although Fel-1 and Fel-2 stimulate the proliferation of T cells, Counsell et al. do not teach or suggest that the administration Fel-1 and Fel-2 alter aberrant, pathogenic antibody production or provide evidence that the administration of such a peptide to a mammal tolerizes T cells.

Norman et al. disclose that subsequent exposure of the IPC-1 and IPC-2-immunized humans to cats resulted in a decrease in nose and lung symptoms in groups treated with 750 μg or 75 μg of the peptides, but not in the group treated with 7.5 μg of the peptides (Figure 2.). However, Norman et al. state that none of the treated groups "showed a significant change in IgE or IgG antibody to Fel d 1" (page 1626, Table 1), and that "T cell proliferation assays to peptides and recombinant Fel d 1 chain 1 and chain 2 did not reveal any consistent alterations attributable to treatment" (page 1626). These results were in contrast to the results in Briner et al. (i.e., the subcutaneous administration of a combination

of IPC-1 and IPC-2 to mice prior to exposure to Fel d 1 resulted in decreased levels of IL-2 secretion by spleen cells, an indication of T cell tolerization), leading the authors to admit that the murine model is "in several ways different from human allergy" (page 1628).

As acknowledged by the Examiner, Norman et al. do not teach or suggest the administration of a peptide to the respiratory tract of a mammal. Moreover, Norman et al. do not teach or suggest that the administration of a particular peptide to a mammal tolerizes T cells, or in any way modulates aberrant, pathogenic or undesirable antibody production in that mammal to an antigen.

Therefore, Norman et al. do not anticipate Applicant's invention. Hence, withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

The 35 U.S.C. §103(a) rejections

The Examiner rejected claims 1-2, 7, 10, and 15-18 under 35 U.S.C. §103(a) as being unpatentable over Norman et al. in view of Metzler et al. (International Immunol., 5, 1159 (1993)), Ma et al. (J. Neuroimmunol., 58, 51 (1995)), and Hetzel et al. (Int. Arch. Allergy Immunol., 107, 275 (1995)). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

As discussed above, Norman et al. do not teach or suggest the administration of an epitope peptide to the respiratory tract of a mammal, e.g., to tolerize T cells or alter aberrant, pathogenic or undesirable antibody production. Thus, Applicant's invention is not obvious in view of Norman et al.

Metzler et al. relate that experimental autoimmune encephalomyelitis (EAE) is a model for acute inflammatory autoimmune disease, such as multiple sclerosis (pages 1159-1160). EAE, which can be induced in mice by administration of the acetylated N-terminal peptide of myelin basic protein (MBP), is a disease in which "$CD4^+$ T lymphocytes play a central role (page 1160, lines 6-7), i.e., EAE a T cell-mediated disease, not an antibody-mediated disease.

Metzler et al. disclose that intranasal, but not oral, administration of an encephalitogenic peptide of MBP, prior to the induction of disease by subcutaneous injection of peptide or spinal cord homogenates, protected H-2^u mice from developing EAE, as measured by the incidence of disease, median day of onset and the mean grade of EAE in test mice versus control mice. There is no data provided in Metzler et al. related to whether peptide administration altered T cell activity or antibody levels.

Prior to Applicant's disclosure it was unclear whether antigen or peptide administration would be efficacious for an antibody-mediated disease for two reasons. First, while effective at reducing antigen-specific CD4+ responses, administration of antigen through routes that downregulate CD4+ responses may directly stimulate B cells specific for the administered antigen (see page 2 of Applicant's specification). This stimulation may have disastrous consequences, as has been shown in marmoset EAE, where intraperitoneal administration of myelin resulted in CD4+ tolerance to myelin, but also in an acute, fatal form of EAE. The fatal form of EAE was characterized by antibody specific for the myelin oligodendrocyte glycoprotein. Second, administration of antigen through routes that stimulate Th2 cells and downregulate proinflammatory Th1 cells can stimulate antibody synthesis and cause exacerbation rather than improvement of antibody-mediated autoimmune diseases. This concern was also noted in Norman et al. with respect to the use of peptides for tolerization (i.e., peptides must be carefully selected to avoid peptides having tertiary structures recognized by IgE antibodies).

Hence, Metzler et al. do not disclose or suggest a method of preventing or inhibiting an indication or disease associated with aberrant, pathogenic or undesirable antibody production. Further, this reference does not disclose or suggest that the administration of a peptide to a mammal results in a reduction in the priming or activity of T cells and/or the antibody response to a given antigen. Nor does reference teach or suggest the use of a peptide comprising a universal, immunodominant epitope sequence. Thus, Metzler et al., alone or taken with the Norman et al., do not render Applicant's invention obvious.

Ma et al. report that nasal administration of *Torpedo* acetylcholine receptor (TAChR) to Lewis rats (an inbred line), prior to the induction of disease with TAChR, suppresses experimental autoimmune myasthenia gravis (EAMG), and tolerizes rats to acetylcholine receptor (AChR). The authors report that not only were disease symptoms inhibited, but that serum anti-AChR IgG antibody levels and T cell proliferation in peripheral lymphoid organs were suppressed after nasal administration of TAChR (Abstract). Ma et al. suggest that the nasal administration of AChR in human MG may be advantageous (page 56).

Ma et al., however, provide no assurance that the administration of a peptide would prevent or inhibit an antibody-mediated disease. Nor would Ma et al. motivate the art worker to administer a peptide to a mammal since the administration of full length TAChR resulted in tolerization. Furthermore, Ma et al. do not teach or suggest the use of a universal, immunodominant epitope peptide to treat a disease associated with aberrant, pathogenic or undesirable antibody production. Thus, Ma et al., alone or in combination with Norman et al. and Metzler et al., do not render Applicant's invention obvious.

The Hetzel et al. review suggests that, as Th1 cells mediate macrophage activation and delayed-type hypersensitivity (DTH) and Th2 cells provide help for B cells and stimulate eosinophilia, the deviation of effector function from Th2 to Th1 by peptides may be useful in immunotherapy. Hetzel et al. note that in a murine system of *in vivo* tolerance to the house dust mite allergen Der p1, oral or nasal exposure to a peptide containing a dominant T cell epitope of Der p1 rendered naive and primed (inbred) mice unresponsive to challenge with Der p1 (citing to Hoyne et al., J. Exp. Med., 178, 1783 (1993), copy enclosed). In concluding, Hetzel et al. caution that while strategies for immunotherapy of allergic diseases have been developed in animal models, "their efficacy in the human clinical context remains to be determined" (page 277). The authors do not provide any discussion of the reasons why the results from a murine model are not readily extrapolated to humans, but instead refer to their interest in the duration of specific T cell tolerance and the feasibility of down regulating an ongoing allergic response.

The present invention is directed to the use of a universal, immunodominant epitope sequence to tolerize mammals to an antigen associated with aberrant, pathogenic or undesirable antibody production. In contrast, the *in vivo* results referred to in Hetzel et al. were obtained from only one strain of inbred mice and so would not be indicative of efficacy in humans or other non-inbred mammals. Thus, Hetzel et al., alone or in combination with Norman et al., Ma et al., and Metzler et al., do not render Applicant's invention is not obvious.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the art must provide a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. In re Ochiai, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1997); M.P.E.P. §§2142, 2143.

Although nasal administration of a peptide was reported to tolerize mice in Hetzel et al., the results were obtained from inbred mice, and such results are not necessarily indicative of results for any other organism, e.g., non-inbred organisms. As for Norman et al., the subcutaneous administration of a combination of peptides appeared to decrease nose and lung symptoms in cat-sensitive humans, but did not effect either antibody synthesis or T cell proliferation. Moreover, the results reported in Metzler et al. relate to a T cell-mediated disorder, and cannot be employed to predict success for an antibody-mediated disorder. Further, Ma et al. employed whole antigen administration to inbred mice. Therefore, the art worker in possession of the cited art would have no reasonable expectation that respiratory administration of a peptide can prevent or inhibit an indication associated with aberrant, pathogenic or undesirable antibody production or tolerize T cells in mammals, e.g., mammals that are divergent at their immune response loci.

The Examiner asserts that one of ordinary skill in the art would have been motivated to substitute the nasal administration of Metzler et al. for the subcutaneous administration of Norman et al., or by the suggestion in Hetzel et al. that nasal therapy would be practical and enable self-administration. However, the Examiner is requested to note that Hetzel et al. actually state that nasal or oral therapy would have both advantages. The teachings in the cited art cannot be combined to arrive at Applicant's invention as there is no direction in the cited art as to which route of administration (nasal, oral or subcutaneous) or which tolerogen (peptide or antigen) should be employed to alter aberrant, pathogenic or undesirable antibody synthesis or tolerize T cells. In combining the cited references, Applicant respectfully asserts that the Examiner has used the above-identified application as a guide. However, care should be taken avoid to hindsight reconstruction by using an Applicant's disclosure "as a guide through the maze of prior art references, combining the right references in the right way" so as to achieve the result of the claims at issue. See, Grain Processing Corp. v. American Maize-Products Co., 840 F.2d 902, 5 U.S.P.Q. 2d 1788 (Fed. Cir. 1988). Using Applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of 35 U.S.C. § 103 of judging obviousness at the point in time when the invention was made. *Id.* Thus, the combination of the cited art does not render Applicant's invention obvious.

The Examiner also rejected claims 1-5, 8, 11-15, 17-18, and 31 under 35 U.S.C. § 103(a) as being unpatentable over Ma et al., in view of Moiola et al. (J. Immunol., 152, 4686 (1994)), and Bellone et al. (Eur. J. Immunol., 21, 2303 (1991)). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

As discussed above, Ma et al. disclose the nasal administration of whole AChR to suppress EAMG in Lewis rats. Ma et al. provides no assurance that administration of a peptide would suppress EAMG or any other disorder.

To determine whether CD4+ cells from myasthenia gravis (MG) patients recognize one or several epitopes within an immunodominant region, Moiola et al. employed

four 20-amino acid residue peptides from either the α or γ subunit of human AChR to propagate CD4+ lines from MG patients. The stimulation of the cell lines by single residue substituted peptides of these 4 peptides ("analogues") was used to determine whether the cell lines were polyclonal and recognized overlapping epitopes. The results showed that within the 20 residues, the same sequence is involved in the formation of epitopes, even in DR-discordant patients.

In the discussion section, Moiola et al. note that "[i]mmunosuppressive approaches based on the use of peptide analogues of autoimmune epitopes or on TCR-targeted immunosuppression at Ag-specific Th cells have been successfully used for treatment of autoimmune experimental encephalomyelitis (EAE)". However, the authors admit that the "large number of AChR sequences forming CD4+ epitopes in MG patients casts some doubts about the feasibility of similar immunosuppressive approaches in this disease" (page 4696). The authors speculate that if the epitope repertoire of Th cells involved in the synthesis of pathogenic antibodies is more limited than that detected by testing CD4+ cell proliferation *in vitro*, the CD4+ immunodominant regions are "potentially useful for development of peptide analogues able to inhibit pathogenic T cell response" (page 4697). Nonetheless, there is nothing in Moiola et al. that provides the art worker with a reasonable expectation that the administration of a peptide could inhibit or prevent a disease such as MG, e.g., by tolerizing T cells and/or altering aberrant, pathogenic or undesirable antibody production in a mammal. Furthermore, Moiola et al. do not disclose or suggest respiratory administration of any agent, much less a peptide having a universal, immunodominant epitope. Thus, Moiola et al., alone or with Ma et al., do not render Applicant's invention obvious.

Bellone et al. prepared overlapping synthetic peptides corresponding to the complete sequence of the α subunit from TAChR and murine AChR (MAChR), in order to map T helper epitopes in congenic mice strains having different H-2 haplotypes, i.e., C57BL/6 ($H\text{-}2^b$), CB17 ($H\text{-}2^b$), BALB/c ($H\text{-}2^d$), and BALB/B ($H\text{-}2^d$). The mice were immunized subcutaneously with TAChR. Total T cells ("T-Tot" are a population of cells derived from

spleen cells that have been enriched for T cells) and L3T4+ (helper) cells from the immunized mice were induced to proliferate with individual peptides. For individual TAChR peptides, the "same peptides were recognized by both cell populations and no peptide was recognized exclusively by the T-Tot population" (page 2306, Figure 2). T cells from C57BL/6 and BALB/B mice did not cross-react with any of the individual MAChR peptides (page 2307). In contrast, T cells from BALB/c and CB17 mice cross-reacted with one MAChR peptide (page 2307). The authors found no overlap in the T repertoire of mice of H-2^b and H-2^d haplotype (page 2308).

Thus, Bellone et al. do not teach or suggest a universal epitope peptide, much less the use of such a peptide to tolerize a mammal to an antigen. Nor does Bellone et al. disclose or suggest respiratory administration of a peptide to a mammal. Finally, although Bellone et al. do point out that certain regions of AChR are conserved in humans, mice and *Torpedo*, this reference does not provide any evidence that the administration of any peptide of AChR can tolerize a mammal and/or alter antibody production. Therefore, Bellone et al. do not disclose or suggest Applicant's invention, nor remedy the deficiencies of Ma et al. and Moiola et al.

The Examiner asserts that the art worker would be motivated to substitute the peptide of Moiola et al. and Bellone et al. for the whole antigen administration of Ma et al., and that all three references provide the art worker with a reasonable expectation that peptide administration would inhibit MG. However, the Examiner is requested to note that the murine T cell epitopes for the α subunit of TAChR for Balb/B and CB17 mice are residues 1-20 and 304-322 (both strains are H-2^b), for Balb/c mice are residues 150-169 and 360-378, and for C57BL/6 150-169, 181-200, 182-198 and 360-378 (see Table 2 of Bellone et al.), while Lewis rats recognize residues 73-90, 97-112, 100-116, 127-143, 389-409, and 426-437 (see Lennon et al., Proc. Natl. Acad. Sci. USA, 82 8805 (1985) and Lennon et al., Ann. N.Y. Acad. Sci., 505, 439 (1987), a copy of each is enclosed), i.e., the T cell repertoires of mammals, which have different haplotypes at the immune response loci, for the same antigen are different. Therefore,

one of ordinary skill in the art in view of the cited art would have no reasonable expectation that an individual peptide could be identified which would be useful to tolerize mammals, and/or alter antibody production in mammals, in mammals that are divergent at the immune response loci.

Moreover, only Ma et al. disclose an agent, i.e., whole antigen, that tolerized a rat against EAMG. Moiola et al. and Bellone et al. describe peptide-induced proliferation of T cells, not the use of peptides for tolerization. Further, none of the cited references discloses or suggests the use of a peptide comprising a universal epitope, much less that respiratory administration of a such peptide can prevent or inhibit an indication or disease associated with aberrant, pathogenic or undesirable antibody production or tolerize T cells. In fact, the teachings in Moiola et al. and Bellone et al., that the T cells of MG patients recognize a large number of CD4+ epitopes and that there was no overlap in the T cell repertoire in H-2 divergent mice, respectively, would lead one of ordinary skill in the art to conclude that is was unlikely that a peptide could be identified that would be recognized by MHC divergent individuals. Thus, the requisite motivation to substitute a peptide for whole antigen is not provided by the cited art, i.e., Moiola et al. or Bellone et al.

Hence, the combination of the Ma et al., Moiola et al., and Bellone et al. do not render the Applicant's invention obvious.

Thus, Applicant respectfully requests that the Examiner withdraw the 35 U.S.C. § 103(a) rejections of the claims.

It is respectfully submitted that the claims are in condition for allowance and notification to that effect is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents, Washington, D.C. 20231 on **August 17, 1999**.

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